UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,865	09/28/2000	Erwin Gelfand	2879-68	9468

22442 7590 10/23/2002

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/672,865	GELFAND ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *3,5,7-13,15,16,20,21,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,14,17-19 and 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VIII in Paper No. 10 is acknowledged. The traversal is on the ground(s) that a thorough search for group VIII should also include the subject matter of groups I-VII and IX-XI, that although the agents used in different methods are not structurally related, they have a common general functional relationship that are linked by claims 1-5 and 17-19, therefore there would not be an undue burden on the Examiner to examine all the claims. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods of reducing airway hyper-responsiveness in a mammal comprising increasing γδ T cell action in a mammal by administering *in vivo* to said mammal an agent that activates γδ T cells in said mammal, wherein said cells could be activated via different signaling pathways, the agent is selected from numerous types of proteins, such as a BiP-binding motif, glycosylated protein, a randomly synthesized heterocopolymeric peptide composed of glutamic acid and tyrosine, a mycobacterial product, a cardiolipin; various antibodies and antibody conjugates, cytokines and nucleic acids. These agents belong to distinct chemical entities; have distinct and diverse physiological functions in addition to activating said cells, and distinct mode of operation with regard to their biodistribution and pharmacokinetics *in vivo*. A serious search burden would be imposed on the Office if all groups were examined together. Further, the use of the divergent therapeutic

agents require distinct technical considerations, for example, the oligonucleotide used in group IV is not used in group VIII, and requires distinct search and technical consideration compared to TNF-α. The *ex vivo* step of group XI is not required in groups I-X. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter (DNA, protein, bacterial derivatives, antibodies, etc.) and are thus, separately classified and searched. Further search of these inventions is not co-extensive, as indicated by the separate classifications. With regards to inventions XIII and XII, the argument is persuasive; the two groups will be rejoined if filed in a divisional application. In conclusion, the requirement as now modified is deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-35 are pending, however, claims 3, 5, 7-13, 15, 16, 20, 21, 34, and 35 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1, 2, 4, 6, 14, 17-19, and 22-33 are under current examination.

Priority

This application claims the benefit of priority to application serial number 60/157,231. However, the subject matter of instantly elected invention, drawn to a method of reducing airway hypersensitivity in a mammal comprising administration of TNF-α is first disclosed in this application. The Examiner has established a priority date, i.e. 9/30/2000, the filing date of instant application. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Objections

Claims 1, 2, 4, 6, and 17-19, 22-25 are objected to because of the following informalities: the claims encompass more than one invention as defined in Paper #8, upon election of an invention for examination, said claim should be amended to the extent that it reads upon the elected invention. For the purpose of compact prosecution, the claims will be examined to the extent that reads on the elected invention.

Claim 1 is objected to because it is not a complete sentence, there is no verb in the phrase.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6, 14, 17-19, and 22-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to a method to reduce airway hyper-responsiveness (AHR) in a mammal, comprising increasing $\gamma\delta$ T cell action by administering tumor necrosis factor-α (TNF-α) to a mammal that has or is at risk of developing a respiratory condition associated with airway hyper-responsiveness (including asthma, chronic obstructive pulmonary disease, allergic bronchopulmonary diseases, Specification, page 10, lines 18-25). Given the broadest reasonable interpretation, these claims clearly read on a therapeutic method. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable

interpretation that is consistent with the specification. "a method to reduce airway hyperresponsiveness in a mammal" is defined as a method, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, the claims will be evaluated by that standard.

In view of the guidance provided, the specification teaches that the present inventors have discovered that γδ T cells can regulate airway function in a γδ T cell-dependent manner and identifying them as important cells in pulmonary homeostasis; that TNF-α is a particularly effective mediator of γδ T cell activation in cell cultures (paragraph bridging pages 29-30). In a set of experiments performed in TNF-α deficient and transgenic mice, the specification teaches that the number of γδ T cells in the lung of TNF-α deficient mice was significantly lower than in normal C57BL/6 mice whereas it increased significantly in TNF-α transgenic mice compared to wild type littermates (paragraph bridging pages 60-61); that mice genetically deficient in TNF-α developed AHR to a greater extent than the C57BL/6 mice (paragraph bridging pages 58-59), that administration of TCR-δ mAb suppressed the numbers of γδ T cells in the lung of TNF-α transgenic, as well as C57BL/6 and wild type littermates (C57BL/6). Therefore, the specification seems established a correlation between the γδ T cells, the levels of TNF-α, and the AHR in certain aspects. However, it is noted that the degree of airway cellular inflammation is *similar* between TNF-α deficient, transgenic (overexpressed), or inbred C57BL/6 mice (page 61, lines 17-21), and the specification is silent with regard to how TNF-α is to be administered, and its effect on AHR when administered to a subject suffering the disease.

In view of the state of the art and levels of the skilled in the art, TNF-α is known to have diverse physiological effects *in vivo*, particularly as an immune modulator and mediator in immune response. However, it is also known for its severe adverse effects, particularly as a mediator of endotoxic shock, inflammatory joint disease, immune deficiency states, allograft rejection, and some parasitic infections. As a therapeutic agent, TNF-α has been used in cancer therapies for advanced cases, however, its efficiency has not been proved even though it is backed by solid theoretical bases (*Jones et al*, Prig Growth Factor Rees 1989;1:107-22). With respect to TNF-α in airway hypersensitivity, it is known that decreased γδ T cells in the peripheral blood is associated with allergic asthmatic individuals (Chen, Clint Exp Allergy 1996;26:295-302, IDS/12), that γδ T cells respond strongly to TNF-α treatment in vitro (IDS/21), that IgE levels could be regulated by TNF-α through many other cytokines and co-stimulatory factors. For example, *Yanagihara*, (Allergol Intl 1999;48:111-9) teaches, "ALTHOUGH REGULATION OF GERMLINE Cε TRANSCRIPTION BY CYTOKINES, SUCH AS IFN-G, TNF-A, AND TRANSFORMING GROWTH FACTOR-B, CORRELATES WELL WITH LEVELS OF IGE PRODUCTION, ADDITIONAL COSTIMULATORY MOLECULES, INCLUDING CD40L, ARE REQUIRED FOR THE INDUCTION OF IGE ISOTYPE SWITCHING" (right column of page 113). Evidently, TNF-α contributes to the regulation of airway hypersensitivity or AHR in a complicated fashion. Although the deficiency of TNF-α increases the severity of AHR, the overexpression of TNF-α in recited transgenic mice fails to reduce the AHR associated inflammation, therefore, the outcome of administration of TNF-α on AHR population is highly unpredictable, would result in a trial and error situation. It is also noted that claims 30 and 31 set forth specific

parameters regarding the degree of the airway responsiveness before and after treatment. However, such parameter lacks support in the specification because the specification is silent regarding *in vivo* administration of TNF-α, and the histological study discloses equal degree of inflammation in airway tissue surroundings, it is unclear how such specific numbers could be generated without actual experimentation.

Furthermore, the positive conclusions drawn from transgenic and genetically TNF-α deficient mice are not predictable for a wild-type subject receiving a therapeutic dose of TNF-α via any route of administration. This is because the genetic background is distinct among transgenic, genetically deficient, and normal or AHR population, that it is the general knowledge in the art a transgene could influence many aspects of the transgenic animal, *Nebert et al* (Biochemical Pharmacol 1997 Feb;53:249-54) teach the "neighborhood effect" in genome modification between different mouse strains, "IT HAS BECOME INCREASINGLY APPRECIATED THAT (A) JUST WHERE A TRANSGENE IS INSERTED, (B) HOW MUCH OF THE GENE SEGMENT IS REMOVED, AND (C) HETEROGENEITY OF THE GENETIC BACKGROUND OF THE KNOCKOUT LINE CAN ALL CONTRIBUTE TO DRAMATICALLY DIFFERENT PHENOTYPES. IT SHOULD BE APPRECIATED THAT, FOR EXAMPLE, A C57BL/6J (FROM JACKSON LABORATORY) AND A C57BL/6N (FROM NIH) HAVE DIVERGED FROM ONE ANOTHER FOR MORE THAN 45 YEARS AND, THEREFORE, SHOULD NOT BE CONSIDERED GENETICALLY IDENTICAL. Therefore, it is most likely that TNF-α transgenic or deficiency may influence not only the TNF-α secretion, but many other aspects of the immune response of the host as well. Thus, it is highly unpredictable whether phenotypic correction of TNF-α alone would affect the outcome of AHR.

The claimed invention additionally reads on administering the TNF-α via any route of administration, including systemic and locally to the lung tissue. *Kreig et al* (US 6,429,199) teach, "SOME ACTIVATORS OF DENDRITIC CELLS LIKE LPS OR INFLAMMATORY CYTOKINES (TNF) HAVE DOSE LIMITING TOXICITY, WHICH MAKES THEIR SYSTEMIC USE FOR THIS PURPOSE NOT PRACTICAL" (column 25, lines 30-33). In view of such, the systemic administration does not seem to be enabled in the absence of clarification of the contradictory evidence found in the reference.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* therapeutic effect for AHR, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* therapy with TNF-α, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 14, 17-19, and 22-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 4 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the means of manipulating γδ T

cells. Claims 1, 2, and 4 provide for increasing the number or action of γδ T cells, but the claim does not set forth any step involved in the method/process, it is unclear how such increase or activation are achieved. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 4, 6, 14, 17-19, and 22-25 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,429,199 and as evidenced by *Lahn et al* (IDS/21).

The reference applies because applicant's method is broadly claimed (comprises), not limited to administration of TNF-α alone.

Kreig et al teach a method comprising administration of TNF-α in conjunction with CpG oligonucleotide (column 25, lines 1-9) for the immunotherapy of cancer, infectious disease, and allergic diseases including allergic asthma (AHR, column 12, line 59) in a mammal (column 16, lines 17-19), in a pharmaceutically acceptable formulation (column 24, lines 19-27), wherein the formulation is suitable for aerosol delivery (column 24, line 66) to the lung tissue. Because the γδ T cells are sensitive to TNF-α as evidenced by *Lahn et al*, the method would intrinsically target these cells. Thus, *Kreig et al* anticipate the instant claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
October 18, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER